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Use of Antipsychotic Medications in Non-Substance-Related Delirium—the Gap Between Research Findings and Clinical Practices

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Abstract

Purpose of the review Gaps exist between the research knowledge base and clinical practices pertaining to the use of antipsychotics in delirium. We reviewed 19 major randomized studies on the use of antipsychotics in non-substance-related delirium to understand factors contributing to this gap.
Recent findings Based on limited literature, antipsychotics are not effective in treating delirium in patients who are mechanically ventilated intensive care unit patients and those in palliative care, but they may be effective in preventing delirium in high-risk patients after elective surgery. The literature on the use of antipsychotics for delirium in general hospital patients is less clear.
Summary Delirium is a complex and heterogeneous syndrome and is influenced by several individual and clinical factors, which make researching its pharmacological treatment very difficult. Furthermore, heterogeneity of the studies is a barrier to reliable meta-analyses. Until methodologically sound literature pertinent to specific patient populations and clinical scenarios accumulates, we should use both the research literature and clinical expertise to formulate practice guidelines.

Introduction

Delirium is a syndromal manifestation of cerebral dysfunction resulting from a range of diverse reasons that are pathological in nature or disruptive to the biochemical processes of the body. It is characterized by a disturbance in attention and awareness that develops over a short period of time, tends to fluctuate over the course of the day, and is accompanied by at least one other disturbance in cognition involving memory, orientation, language, visuospatial ability, or perception [1]. The DSM-5 suggests five diagnostic specifiers namely substance intoxication delirium, substance withdrawal delirium, medication-induced delirium, delirium due to another medical condition, and delirium due to multiple etiologies. Patients with delirium may be in a state of psychomotor agitation (hyperactive delirium), lethargy and stupor (hypoactive delirium), or fluctuate between these two states (mixed delirium). Delusions and hallucinations are not required diagnostic features of delirium but often occur in its mixed subtype [2•]. The prevalence of delirium varies dramatically based on the patient population and the method of assessment and ranges between 10–31% in general hospital settings [3], 30–80% [4] in critical care settings, and 13–88% in palliative care settings [5].

The standard prevention and management strategies for delirium incorporate treating the underlying cause(s), offering supportive and non-pharmacological interventions, and using medications to control acute symptoms. Medications used for symptomatic management of delirium in diverse clinical settings include antipsychotics, benzodiazepines, antiepileptics, and melatonin-regulating agents. The use of these medications in delirium is off-label as none has a formal regulatory approval.

Historically, haloperidol was the preferred medication for symptomatic management of non-substance withdrawal delirium due to its known efficacy for psychosis, better side effect profile than benzodiazepines and low-potency antipsychotics, and the ease of administration because of availability in both oral and parenteral forms [6]. With the advent of second-generation antipsychotics, they were studied for delirium as an alternative to haloperidol. Despite limited data on their efficacy, haloperidol and the relatively older second-generation antipsychotics including risperidone, olanzapine, and quetiapine are now among the commonly used antipsychotics for symptomatic management of non-substance withdrawal delirium [7, 8••].

The use of antipsychotics in non-substance-related delirium remains a matter of debate with several questions still unanswered [8••, 9]. Over the last few years, some studies and meta-analyses have raised doubts about the efficacy of antipsychotics in delirium. For example, Neufeld et al. [10] systematically reviewed the literature published between 1988 and 2013 and identified 19 studies that met their inclusion criteria. They found that antipsychotic use was not associated with change in delirium duration, severity, or hospital or intensive care unit (ICU) length of stay. Similarly, the current clinical practice guidelines on management of delirium in adult ICU patients noted that there was no published evidence to support that haloperidol reduced duration of delirium in ICU patients, and only one small study suggested quetiapine may reduce the duration [11]. In contrast, other meta-analyses have found that antipsychotics are better than placebo for prevention and treatment of delirium [12, 13]. In practice, antipsychotics are still used for delirium in diverse clinical settings and are often recommended in institutional guidelines [14]. Antipsychotics are the most studied agents to prevent and treat delirium, but it is difficult to translate research findings into clinical practice [8••]. We undertook this review to better understand this dilemma. We briefly describe the randomized-controlled studies on the use of antipsychotics for treatment or prevention of delirium as well as the randomized studies that compared antipsychotics without a control group and then highlight factors based on these studies that make it difficult to draw reliable clinical guidance from their findings.

Treatment

Use of antipsychotics to treat or prevent delirium

We searched PubMed for English literature from last 10 years using search terms "antipsychotic" and "delirium." From the titles of the search results, we identified several studies and meta-analyses of interest and reviewed their abstracts. We also

reviewed the reference lists of several recent meta-analyses. We identified 19 randomized studies on the use of antipsychotics in delirium—five studies compared antipsychotics with placebo for treatment of delirium [15–19], six studies compared antipsychotics with placebo to prevent delirium [20–25], and eight studies compared various antipsychotics with each other without a control group [26–33].

Studies on the use of antipsychotics for treatment of delirium

We identified five randomized-controlled studies that compared antipsychotics with placebo for the treatment of delirium (Table 1) [15–19]. Two of these studies were conducted on mechanically ventilated ICU patients with haloperidol as the active agent in one [18] and haloperidol and ziprasidone as active agents in the other [17]. In both these studies, active agents did not offer benefit over placebo in terms of number of days in delirium, number of days without delirium, resolution of delirium, the length of stay in the ICU, or mortality. Another ICU study had a mixed patient population, but over 70% of the patients were intubated upon admission to the ICU [16]. In this study [16], the quetiapine group fared better than the placebo group in terms of delirium-free days and time to resolution of delirium, but the duration of ICU stay was similar for both groups. One study included patients from medical and surgical wards [19]. Forty-five percent of the patients had undergone surgery, mostly for orthopedic reasons. Patients in the quetiapine group recovered significantly faster than patients in the placebo group in terms of delirium severity. Lastly, one study was conducted with palliative care patients [15]. Most patients had the diagnosis of cancer. At the 3-day study end, the delirium symptom scores were significantly higher in patients receiving risperidone or haloperidol than patients receiving placebo. Overall, these data suggest that antipsychotics are not effective in treating delirium in patients who are mechanically ventilated ICU patients and in palliative care, but may be effective in treating delirium in general medical and surgical patients (Table 1).

Randomized-controlled studies on the use of antipsychotics to prevent delirium

We identified six studies that compared antipsychotics with placebo to prevent delirium in high-risk patients [20–25] (Table 2). Two studies used haloperidol [21] and olanzapine [23], respectively, as active agents for prevention of delirium after elective orthopedic surgery. Although the active agents offered significant benefits over the placebo on many measures of delirium, these benefits were not consistent across the studies. The incidence of delirium in the study using haloperidol was comparable to placebo, but it was significantly lower than placebo in the study using olanzapine. In contrast, delirium duration was briefer with haloperidol but longer with olanzapine, in comparison with placebo. A lower incidence of delirium was also noted in patients who received prophylactic haloperidol after gastrointestinal surgery than those who received placebo [22]. In another study of patients who had undergone cardiac surgery, risperidone significantly decreased the incidence of delirium compared with placebo [24]. In another study, elderly ICU patients (> 85 years age) who had undergone non-cardiac surgery were randomized to receive a small prophylactic dose of haloperidol or placebo over the initial 12-h after surgery [25]. If delirium developed, it was handled with non-pharmacological interventions first and open-label haloperidol was reserved for severe agitation. The haloperidol group fared

Table 1. Randomized-controlled trials on the use of antipsychotics to treat delirium [15–19]

Study, location, and agents	Patient population/assessment tools	Major findings
Page et al. (2013) [18] ICU Haloperidol and placebo	ICU patients needing mechanical ventilation within 72 h of admission randomized to receive haloperidol 2.5 mg intravenously every 8 h ($N = 71$; mean age 68 years) or placebo ($N = 70$, mean age 68 years). CAM-ICU and RASS were used to monitor delirium and level of sedation, respectively. Patients in both groups were allowed to receive open-label haloperidol or another antipsychotic.	During the 14-day trial, patients in the haloperidol group (median 5 days) and the placebo group (median 6 days) spent about the same number of days without delirium and without coma or in delirium (median 5 days for both groups). After 28 days, the groups did not differ in the length of critical care stay, length of hospital stay, and mortality. The need for additional antipsychotic treatment was significantly higher for the placebo group (18 patients) than the haloperidol group (8 patients). No serious adverse events were attributable to the study drug.
Girard et al. (2010) [17] ICU Haloperidol, ziprasidone, and placebo	Mechanically ventilated ICU patients were randomized to receive haloperidol 5 mg ($N = 35$, mean age 51 years), ziprasidone 40 mg ($N = 30$, mean age 54 years), or placebo ($N = 36$, mean age 56 years) followed by a second dose in the same amount 12 h later. Subsequent doses were administered every 6 h until clinical changes prompted a change in the dose. Open-label, as-needed use of haloperidol was allowed for all groups. CAM-ICU and RASS were used to monitor delirium and the level of sedation, respectively.	Compared with the placebo, haloperidol or ziprasidone did not increase the number of days patients were alive without delirium or coma. The daily delirium risk and the duration of delirium and coma were similar among treatment groups. Daily sedation goals were also similar for all the groups throughout the study. No differences were found in ventilator-free days, hospital length of stay, and mortality. Fifteen (42%) patients in the placebo group, 7 (20%) patients in the haloperidol group, and 10 (33%) patients in the ziprasidone group received an antipsychotic in addition to the study agent ($P = 0.14$). No serious adverse event occurred during the trial.
Devlin et al. (2010) [16] ICU Quetiapine and placebo	ICU patients were randomized to receive either quetiapine ($N = 18$, mean age 62.4 years) or placebo ($N = 18$, mean age 63.6 years). Therapy was initiated at 50 mg every 12 h administered orally or through the nasogastric tube and incrementally increased to a maximum of 200 mg every 12 h if needed. Patients in both groups were allowed to receive intravenous haloperidol 1–10 mg up to every 2 h on an as-needed basis. Patients were screened with ICDSC and monitored with ICDSC and SAS.	The time to first resolution of delirium was shorter with quetiapine than placebo (median 1 day versus 4.5 days $P = 0.001$). Over the 10-day study period, delirium resolved at least once in all quetiapine patients versus 78% of patients receiving placebo ($P = 0.05$). Quetiapine group spent fewer hours in delirium (36 versus 120 h; $P = 0.006$) and fewer hours in agitation (6 versus 36 h; $P = 0.02$) than the placebo group. Quetiapine group received a shorter duration of haloperidol therapy than the placebo group (3 versus 4 days; $P = 0.05$), but the amount/day did not differ. Duration of mechanical ventilation, length of ICU and hospital stay, and hospital mortality was similar between groups. Five episodes of somnolence and one episode of hypotension were possibly related to the use of quetiapine.

Table 1. (Continued)

Study, location, and agents	Patient population/assessment tools	Major findings
Tahir et al. (2010) [19] General hospital Quetiapine and placebo	Of the 42 patients, 19 had undergone surgery (mostly orthopedic), and others had medical reasons. Patients were randomized to receive quetiapine ($N = 21$, mean age 84.1 years) or placebo ($N = 21$, mean age 84.3 years). DRS-R-98 was used to screen and monitor for delirium. Secondary outcome measures included MMSE, BPRS, and CGI. Follow-up assessments done on days 1, 2, 3, 4, 7, and 10 dictated the dosing regimen.	The highest mean dose of quetiapine was 40 mg on day 4 (day 1 = 25 mg, day 10 = 37.50 mg). On day 3, the non-cognitive symptoms of delirium improved significantly in the quetiapine group, but the total mean DRS-R-98 score was comparable for both groups at individual time points. The differences in rate of improvement between the two groups for DRS-R-98 scores suggested that patients in the quetiapine group improved more quickly than the placebo group ($P = 0.026$). Quetiapine treatment was stopped in one patient due to sedation.
Agar et al. (2017) [15] Palliative care Risperidone, haloperidol, and placebo	Terminal patients mostly with a diagnosis of cancer who had delirium were randomized to receive risperidone 1 mg ($N = 82$, mean age 74.5 years), haloperidol 1 mg ($N = 81$, mean age 76.5 years), or placebo ($N = 84$, mean age 73.8 years) orally followed by a maintenance dose of 0.5 mg every 12 h. Patients ≥ 65 years of age received half the dose. Delirium was monitored with MDAS and NuDESC. All patients received individualized nonpharmacologic care and subcutaneous midazolam for severe distress.	34 patients died during the 72-h study period (9 in the placebo group, 9 in the haloperidol group, 16 in the risperidone group). In the primary intention-to-treat analysis, delirium symptom scores at the end of the study were significantly higher in the risperidone ($P = 0.02$) and haloperidol ($P = 0.009$) groups than the placebo group. MDAS scores were higher in the active treatment groups reaching significance for the risperidone group ($P < 0.01$) but not for the haloperidol group ($P = 0.06$). The incidence of EPS was higher in the risperidone ($P = 0.03$) and haloperidol groups ($P = 0.01$) than the placebo group. Midazolam use was comparable between groups.

BPRS, Brief Psychiatric Rating Scale; *CAM-ICU*, Confusion Assessment Method for ICU; *CGI*, Clinical Global Improvement; *DRS*, Dementia Rating Scale; *DRS-K*, Delirium Rating Scale-Revised-98-Korean version; *DRS-R-98*, Dementia Rating Scale Revised-1998; *EPS*, extrapyramidal side effects; *ICDSC*, Intensive Care Delirium Screening Checklist; *MDAS*, Memorial Delirium Assessment Scale; *MMSE*, Mini Mental Status Examination; *NuDeSC*, Nursing Delirium Screening Scale; *MSAS*, Modified Simpson–Angus Scale; *RASS*, Richmond Agitation-Sedation Scale; *SAS*, Sedation-Agitation Scale

better than the placebo group on all measures of delirium used in the study. Finally, in one study, patients who developed subsyndromal delirium after on-pump cardiac surgery, the incidence of delirium was significantly lower with risperidone than placebo [20]. Overall, these data suggest that haloperidol, olanzapine, or risperidone prophylaxis benefit postoperative patients in diverse surgical situations (Table 2).

Randomized studies without a control group comparing various antipsychotics in delirium

We included eight randomized studies that compared two or more antipsychotics with each other without a placebo control group [26–33] (Table 3). Antipsychotics researched in these studies included amisulpride, chlorpromazine, haloperidol, olanzapine, quetiapine, and risperidone. The patient

Table 2. Randomized-controlled studies on the use of antipsychotics to prevent delirium [20–25]

Study, location, and agents	Patient population/assessment tools	Major findings
Kalisvaart et al. (2005) [21] Orthopedics Haloperidol and placebo	Hip-surgery patients ≥ 70 years old and at risk for postoperative delirium were randomized to receive haloperidol 1.5 mg/day ($N = 212$, mean age 78.7 years) or placebo ($N = 218$, mean age 79.6 years) preoperatively. The treatment was continued for up to 3 days. Incidence of delirium, severity of delirium, duration of delirium, and the length of hospital stay were measured using CAM and DRS-R-98.	The percentage of patients with postoperative delirium in the haloperidol and placebo groups was similar (15.1 and 16.5%, respectively). The mean highest DRS-R-98 scores for the haloperidol and placebo groups were 14.4 and 18.4, respectively ($P < 0.001$). Delirium duration was 5.4 versus 11.8 days, respectively ($P < 0.001$), and the mean number of days in the hospital was 17.1and 22.6, respectively ($P < 0.001$). No haloperidol-related side effects were noted.
Larsen et al. (2010) [23] Orthopedics Olanzapine and placebo	Patients were aged ≥ 65 years and had undergoing elective knee- or hip-replacement surgery. They were randomized to receive 5 mg of orally disintegrating olanzapine ($N = 196$, mean age 73.4 years) or placebo ($N = 205$, mean age 74 years) immediately prior to the surgery. Screening and monitoring instruments included CAM, MMSE, and DRS-R-98.	The incidence of postoperative delirium was lower in the olanzapine group than in the placebo group for the entire sample (14.3 versus 40.2%; $P < 0.0001$) as well as for the surgical sub-groups. The time-to-onset of delirium was significantly longer ($P < 0.0001$) in the olanzapine group than in the placebo group as a whole. Delirium lasted longer in the olanzapine group than in the placebo group (2.2 versus 1.6 days; $P = 0.02$). No serious adverse events were attributed to use of olanzapine.
Kaneko et al. (1999) [22] Gastrointestinal surgery Haloperidol and placebo	Patients who underwent gastrointestinal surgery were randomized to receive haloperidol 5 mg ($N = 38$, mean age 72.4 years) or normal saline ($N = 40$, mean age 73.1 years) intravenously at 9:00 pm for 5 consecutive days. The assessment after the 5th day of treatment was based on clinical notes with particular attention to signs and symptoms of delirium.	Postoperative delirium began 2 to 4 days after surgery. Overall incidence of delirium was 21.8%. Four of the 38patients (10.5%) in the haloperidol group and 13 of 40 patients in the placebo group (32.5%) developed delirium ($P < 0.05$). No significant adverse effects of haloperidol were observed.
Prakanrattana and Prapaitrakool (2007) [24] Cardiac surgery Risperidone and placebo	126 adult patients undergoing elective cardiac surgery with cardiopulmonary bypass were randomly assigned to receive either 1 mg of risperidone ($N = 63$) or placebo ($N = 63$) sublingually when they regained consciousness. Delirium was assessed using CAM-ICU.	The incidence of postoperative delirium was significantly lower in the risperidone prophylaxis group than the placebo group (11.1 versus 31.7%, respectively; $P = 0.009$). All delirium episodes commenced within the first three postoperative days with the highest incidence being on the day of surgery. No significant drug adverse effects were observed.
Wang et al. (2012) [25] Non-cardiac surgery Haloperidol and placebo	Patients > 85 years age admitted to the ICU after a non-cardiac surgery were randomized to receive haloperidol 0.5 mg IV bolus followed by 0.1 mg/h for 12 h ($N = 229$; mean age 74 years) or placebo ($N = 228$, mean age 74.4 years). Patients were	The incidence of delirium during the 7 days after surgery was 15.3% in the haloperidol group and 23.2% in the control group ($P = 0.031$). The mean time to onset of delirium and the mean number of delirium-free days were

Table 2. (Continued)

Study, location, and agents	Patient population/assessment tools	Major findings
	monitored for delirium for 7 days after the surgery using CAM-ICU. Patients who developed delirium were offered non-pharmacological strategies. Open-label haloperidol was reserved for sever agitation.	significantly longer (6.2 versus 5.7 days; $P = 0.021$; and 6.8 versus 6.7 days; $P = 0.027$, respectively), whereas the median length of intensive care unit stay was significantly shorter (21.3 versus 23.0 h; $P = 0.024$) in the haloperidol group than in the control group. No drug-related side effects were documented.
Hakim et al. (2012) [20] Cardiac surgery Risperidone and placebo	Patients aged ≥ 65 years who experienced subsyndromal delirium (ICDSC score 1–3) after on-pump cardiac surgery were randomized to receive 0.5 mg risperidone ($N = 51$) or placebo ($N = 50$) every 12 h by mouth. Patients were monitored by a blinded observer using ICDSC and those scoring > 3 were assessed by a blinded psychiatrist. Patient in each group who developed delirium were initially treated with risperidone. Haloperidol administered if symptoms persisted.	The incidence of delirium was lower ($P = 0.031$) in the risperidone group (13.7%) than the placebo group (34%). There were no significant differences between the two groups for the duration of clinical delirium, highest score on the ICDSC, need for haloperidol, highest doses of risperidone and haloperidol, or length of ICU or hospital stays. Two (3.9%) patients in the risperidone group experienced EPS ($P = 1.0$). Competing-risks regression analysis showed that failure to treat subsyndromal delirium with risperidone was an independent risk factor for delirium ($P = 0.002$).

CAM, Confusion Assessment Method; *CAM-ICU*, Confusion Assessment Method for ICU; *DRS-R-98*, Dementia Rating Scale Revised-1998; *EPS*, extrapyramidal side effects; *ICDSC*, Intensive Care Delirium Screening Checklist; *MMSE*, Mini Mental Status Examination

populations in these studies were much more diverse and mixed than the patient populations in the placebo-controlled delirium treatment and pro-phylaxis studies we previously summarized. Drug dosing in these studies was flexible that allowed adjusting the study drugs on as-needed basis. Additionally, the as-needed use of parenteral haloperidol or a benzodiazepine was allowed in some studies. In all of these studies, delirium severity improved over the course of the study without any significant differences between the antipsychotics in any given study. One study that had a lorazepam treatment group as well reported worsening of delirium in the lorazepam group [26] (Table 3).

Factors to consider when drawing clinical guidance from the literature

We identified several interrelated factors that should be considered when interpreting the findings of the abovementioned studies from a clinical perspective.

The complexity of delirium and its impact on research findings

Delirium is a heterogeneous syndromal expression of diverse diseases and clinical scenarios, often occurs in patients who have multiple pathologies and are on multiple medications, and is influenced by individual factors such as age,

Table 3. Randomized studies without a control group comparing various antipsychotics in delirium [26–33]

Study/agents	Patient population/assessment tools	Major findings
Maneeton et al. (2013) [31] Quetiapine and haloperidol	Medically ill patients with delirium were randomized to receive flexible doses of quetiapine (25–100 mg/day; $N = 24$, mean age 56.6 years, mean daily dose 67.6 mg) or haloperidol (0.5–2.0 mg/day; $N = 28$, mean age 57 years, mean daily dose 0.8 mg). Other psychotropic medications were prohibited. CAM was used to screen and DRS-R-98, CGI-I, and MSAS were used to monitor patients.	Over the 7-day trial period, the mean DRS-R-98 severity scores decreased in each group similarly. The decrease in the DRS-R-98 non-cognitive and cognitive subscale scores was also comparable. At study end, the response and remission rates, the total sleep time, and the MSAS scores were also not significantly different between the groups. Hypersomnia was relatively but not significantly common in the quetiapine-treated patients (33.3%) than the haloperidol-treated group (21.4%).
Yoon et al. (2013) [33] Haloperidol, olanzapine, risperidone, and quetiapine	Eligible general hospital patients with delirium were randomized to receive haloperidol ($N = 23$, mean age 74 years, mean daily dose 1.2 mg), risperidone ($N = 21$, mean age 70.1 years, mean daily dose 1.1 mg), olanzapine ($N = 18$, mean age 69.5 years, mean daily dose 2.9 mg), or quetiapine ($N = 18$, mean age 73.3 years, mean daily dose 47.9 mg). Patients were allowed to receive as-needed intramuscular haloperidol and lorazepam. The efficacy was evaluated using the (DRS-K) and the Korean version of the MMSE.	Over the 6-day study period, the DRS-K severity score decreased and the MMSE (Korean version) score increased significantly ($P < 0.001$ for both) in all groups without any between-group difference. Treatment response rate was lower in patients older than 75 years than in younger patients, particularly in the olanzapine treatment group. The use of as-needed medications was comparable between groups. 15 patients experienced mild side effects (mostly sedation and mild EPS) without any significant differences between the groups.
Grover et al. (2011) [27] Haloperidol, olanzapine, and risperidone	Consecutive eligible general hospital patients with delirium were randomized to receive haloperidol ($N = 21$; mean age 44 years, mean daily dose 0.88 mg), olanzapine ($N = 23$; mean age 45.4 years, mean daily dose 3.05 mg), or risperidone ($N = 20$; mean age 46.5 years, mean daily dose 0.95 mg). As-needed use of the respective medication, haloperidol or lorazepam was allowed. DRS-R-98 and CAM were used to screen and SRS-R-98, MMSE, SAS, AIMS, and UKU were used to monitor patients.	The DRS-R-98 scores decreased and MMSE scores increased significantly ($P < 0.001$ for all groups) over the 6-day study period, but there was no difference between the groups. There was also no between-group difference in the percentage of patients whose DRS-R98 score decreased to < 10. Four patients in the haloperidol group, six patients in the risperidone group and two patients in the olanzapine group experienced mild side effects (mostly sedation and mild EPS).
Kim et al. (2010) [29] Olanzapine and risperidone	Patients with cancer ($N = 23$), femur fracture, head trauma, or pneumonia ($N = 9$) who had delirium were randomized to receive risperidone ($N = 17$, mean age 66.7 years) or olanzapine ($N = 15$, mean age 68.3 years). The mean last observation doses were 0.9 mg/day for risperidone and 2.4 mg/day for olanzapine. As-needed intramuscular haloperidol and lorazepam were allowed. DRS-R-98 was used to monitor delirium.	Significant within-group improvements in the DRS-R-98 score over time were observed at every time point in both treatment groups (all P values < 0.01). There was no significant difference in the change of the DRS-R-98 score from baseline between the treatment groups at any time point. The groups did not differ in terms of response rate (defined as $> 50\%$ reduction from baseline in the DRS-R-98 scores). Mild EPS were observed in 11.8% of risperidone treated and 20% of olanzapine-treated patients.

Table 3. (Continued)

Study/agents	Patient population/assessment tools	Major findings
Lee et al. (2005) [30] Amisulpride and quetiapine	General hospital patients with delirium were randomized to receive flexible doses of amisulpride ($N = 16$, mean age 60.8 years, mean dose 156 mg/day) or haloperidol ($N = 15$, mean age 63.1 years, mean dose 113 mg/day). Other antipsychotics or benzodiazepines were not allowed. Patients were diagnosed clinically and monitored with DRS-R-98.	The mean duration of stabilization as similar for the amisulpride (6.3 days) and the quetiapine (7.4 days) groups. DRS-R-98 scores decreased significantly for both groups without a between-group difference. Similar number of patients in the amisulpride group (81.3%) and the quetiapine group (80%) showed $> 50\%$ reduction in the DRS-R-98 scores. No serious adverse effects were observed.
Han and Kim (2004) [28] Haloperidol and risperidone	Patients from medical units, ICUs and oncology units were randomized to receive haloperidol ($N = 12$, mean age 66.5 years) or risperidone ($N = 12$, mean age 65.6 years). The starting dose was 0.75 and 0.5 mg twice a day, respectively and as adjusted as needed. DRS was used to screen for delirium and MDAS to monitor its severity	The MDAS scores for each group decreased significantly over the 7-day study period ($P < 0.05$). The difference between the groups for the decrease in MDAS scores was not significant. One patient in the haloperidol group experienced mild akathisia. No other significant side effects were observed.
Skrobik et al. (2004) [32] Olanzapine and haloperidol	Adult ICU patients with delirium (mostly surgical) were randomized to receive haloperidol ($N = 45$, mean age 63.3 years, mean daily dose 4.5 mg) or olanzapine ($N = 28$, mean age 67.5 years, mean daily dose 6.5 mg) via the enteral tube (lower dose for patients over the age of 60). Both groups were allowed to receive intravenous haloperidol. Patients were screened with ICDSC and monitored with the Delirium Index.	Just over one-third of patients in each group needed intravenous haloperidol, mostly on the first day. A comparable ($P = 0.83$) significant reduction in the Delirium Index was observed in both groups over time ($P = 0.02$). The dose of benzodiazepines was comparable between the two groups and it decreased over time. None in the olanzapine group and 6 patients in the haloperidol group experienced mild symptoms of EPS.
Breitbart et al. (1996) [26] Haloperidol, chlorpromazine, and lorazepam	Hospitalized patients with AIDS were monitored for delirium. Patients entered the treatment phase of the study if they scored 13 or greater on the DRS. Patients were randomized to receive haloperidol ($N = 11$, mean daily dose 2.4 mg), chlorpromazine ($N = 13$, mean daily dose 50 mg), or lorazepam ($N = 6$, mean daily dose 3 mg). Efficacy and side effects associated with the treatment were measured with repeated assessments using the DRS, MMSE, and ESRS.	Delirium symptoms improved with haloperidol and chlorpromazine treatment but not with lorazepam treatment ($P < 0.07$). Cognitive function improved significantly from baseline to day 2 for patients receiving chlorpromazine. No significant EPS were observed with any treatment. All patients receiving lorazepam developed treatment-limiting adverse effects and the study arm had to be terminated early.

AIMS, Abnormal Involuntary Movement rating scale; *BPRS*, Brief Psychiatric Rating Scale; *CGI-I*, Clinical Global Impression–Improvement; *DRS*, Dementia Rating Scale; *DRS-R*, Dementia Rating Scale Revised-1998; *DRS-K*, Delirium Rating Scale-Revised-98-Korean version; *EPS*, extrapyramidal side effects; *ESRS*, Extrapyramidal Symptom Rating Scale; *ICDSC*, Intensive Care Delirium Screening Checklist; *MDAS*, Memorial Delirium Assessment Scale; *MMSE*, Mini Mental Status Examination; *MSAS*, Modified Simpson–Angus Scale; *SAS*, Sedation-Agitation Scale; *UKU*, Udvalg for Kliniske Undersogelser

degree of morbidity, and history of alcohol use. Because clinical complexity is integral to most cases of non-substance-related delirium, we cannot research it in a population free of confounding risk factors. Furthermore, delirium is a dynamic process. Its severity, course, duration, and outcome depend upon the

causative conditions and their treatment. These factors are very difficult to control in research settings and would impact the study findings [34••]. Current literature suggests that antipsychotics are not better than placebo when delirium is severe and complicated (e.g., in the mechanically ventilated ICU patients) or when its cause is untreatable (e.g., in the palliative care patients), but they may be better than placebo in the relatively less sick general hospital population and after elective surgeries.

The impact of use of as-needed medications

Due to obvious clinical reasons, the placebo-controlled studies of delirium permit the use of as-needed medications, which usually is an antipsychotic, a benzodiazepine, or both. When patients in the placebo group receive as-needed medication(s), it narrows the efficacy gap between the antipsychotic and the placebo groups. For example, in the study by Page et al. [18], haloperidol did not offer benefit over the placebo. However, in this study, 21% of the patients in the placebo group received as-needed haloperidol (versus 8% in the haloperidol group), and the duration of as-needed treatment was significantly longer in the placebo group versus the haloperidol group. Similarly, in the study by Devlin et al. [16], placebo-treated patients required significantly more days of as-needed haloperidol (3–8 days) and a sedative agent (propofol or a benzodiazepine; 1–9 days) than patients treated with quetiapine (2–4 days and 0–3 days, respectively).

The studies may not capture matters of clinical relevance

Current studies on the use of antipsychotics in delirium do not capture a few important clinical aspects. Anecdotally, antipsychotics may help decrease agitation, distress, and combative behavior, but not necessarily and immediately the other symptoms of delirium. As delirium scales are structured to capture broad symptoms [35•], the overall score may not reflect improvement in a few symptoms. The decreased incidence and severity of delirium with the prophylactic use of antipsychotics versus the placebo in the high-risk patients and those with subsyndromal delirium may have been due to decreased agitation and consequent decreased disruption in care, but current literature does not specifically inform us in this regard [20, 36]. Delirium is distressing for the patient and his/her family, so is often also disruptive to clinical care, but current research on the use of antipsychotics in delirium does not capture these aspects as well.

Statistical significance (or lack thereof) may not reflect clinical significance

"Statistical significance" is used to minimize "chance" findings. Several factors drive the "by chance" occurrence(s) and the complexity rises as the number of confounding factors rises. A small sample size, presence of outliers, and how drop-outs are statistically managed can diminish or exaggerate statistical findings further. While statistical significance is important to identify the likelihood that a result occurred by chance, it may not always accurately reflect clinical significance. For example, in the placebo-controlled study by Devlin et al. [16], there was no statistically significant difference between the treatment groups at baseline, but clinically, the placebo-treated group seemed sicker than the quetiapine-treated group with

intubated patients at the start of the study being 89 versus 72% and patients coming from another hospital being 44 versus 11%, respectively. Similarly, in the study by Girard et al. [17], the percent of patients who required as-needed haloperidol (total dose) in the haloperidol, ziprasidone, and placebo groups was 17% (4.5 mg), 30% (10 mg), and 39% (12.5 mg), respectively. One patient (3%) in the haloperidol group, two patients (7%) in the ziprasidone group, and four patients (11%) in the placebo group were administered additional second-generation antipsychotics. None of these differences were statistically significant, but clinically these are meaningful differences that may have impacted the research findings.

Heterogeneity of studies prevents reliable meta-analyses

Current literature on the use of antipsychotics in delirium is heterogeneous in terms of the patient population, nature, and severity of the condition(s) causing delirium, clinical setting, methodology to monitor delirium, doses of the study antipsychotics, allowance of as-needed use of medications, duration of monitoring, and measures of patient outcome. Meta-analyses can provide conflicting results depending upon the studies included/excluded. For example, Fok et al. reviewed the literature on the prophylactic use of antipsychotics in delirium and based on meta-analysis of six studies concluded that antipsychotics reduced the incidence of delirium in several surgical settings, predominantly orthopedic [12]. In contrast, Neufeld et al. performed a meta-analysis of seven studies (five of which were included in the meta-analysis by Fok et al. [12]) and concluded that prophylactic use of antipsychotics did not prevent delirium [10]. Both authors observed heterogeneity between studies. The negative findings by Neufeld et al. [10] seemingly were driven by a study that used a historical no-treatment comparison group [37]. Another similar study has observed mostly positive findings [36], but its data was not included in some of the analysis by Neufeld et al. [10]. This highlights that the findings of meta-analyses on this topic are not consistent and cannot be used reliably for clinical guidance.

Importance of studies comparing various antipsychotics for delirium

Studies that compare efficacy of antipsychotics in delirium without a placebo control group have a major limitation—there is no control group. The limitation is particularly true considering there is no proven effective antipsychotic for delirium that can be used as a comparator. Antipsychotics tend to get grouped together because of their shared approved indications. But in reality, they differ from each other in terms of their neurochemical profile and may differ from each other dramatically when used for other conditions (e.g., in Parkinson's disease psychosis [38]). Well-designed studies comparing antipsychotics in delirium without placebo will help us better define the possible benefits and side effects of antipsychotics in delirium relative to each other.

Discussion

The current literature on the use of antipsychotics in delirium is too heterogeneous and limited to provide a reliable clinical guidance. Limited

literature suggests that antipsychotics are not effective in treating delirium in patients who are mechanically ventilated ICU patients and those receiving palliative care, but they may have a role in managing delirium in general hospital patients. All the studies we reviewed [20–25] and several meta-analysis [12, 39, 40] support the prophylactic use of antipsychotics in high-risk surgical patients, but one meta-analysis [10] has concluded otherwise. So far, the antipsychotics that have consistent (but still limited) evidence for managing or preventing non-substance-related delirium include haloperidol, olanzapine, quetiapine, and risperidone. These data cannot be generalized to other antipsychotics or to substance-related delirium.

Delirium is best managed through a multidisciplinary team approach that includes the patient's family. Antipsychotics should only be considered after non-pharmacological interventions have been offered, and these interventions should continue during the antipsychotic treatment. Symptomatic management of delirium should not draw attention away from investigating and treating the underlying cause(s) of delirium. The decision to use an antipsychotic and the choice and dosing of the antipsychotic should be made on a case-by-case basis. The effectiveness of antipsychotic treatment should be monitored systematically, and the antipsychotic should be withdrawn or substituted if it is ineffective after a few days of treatment. We do not advise continued use of antipsychotics to manage delirium when it is protracted because of a complex etiology or comorbid dementia.

It is essential to monitor antipsychotics for their side effects. From among the four antipsychotics under discussion, haloperidol and risperidone are more likely to cause extrapyramidal side effects and olanzapine and quetiapine are more likely to cause sedation. Much lower doses should be used in elderly patients, as they are prone to extrapyramidal side effects even with second-generation antipsychotics [41, 42]. Haloperidol should not be used in patients with Parkinsonism, and risperidone should be used cautiously in very small doses [41]. Risperidone and to a lesser extent olanzapine and quetiapine may also cause a drop in blood pressure. Olanzapine should be used cautiously in the elderly in view of the few case reports suggesting it can cause delirium in these patients [43–45]. We must also be mindful of warnings from the regulatory agencies about the use of antipsychotics in patients with dementia and the increased risk of QTc prolongation in patients with multi-morbidity taking multiple medications associated with QTc prolongation [46, 47]. The rare likelihood of neuroleptic malignant syndrome should also be kept in mind. It is quite concerning that antipsychotics are continued in significant number of patients after delirium has resolved, and in some cases they are continued even after patient's discharge from the hospital [48•, 49]. Antipsychotics initiated for delirium must be discontinued as soon as delirium resolves.

Researching the pharmacological prevention and treatment of delirium is very difficult due to the heterogeneity, different types and variable course of delirium, absence of biological markers to assess and monitor delirium, numerous confounding factors, and high drop-out rates. A proper placebo-controlled study is essentially impossible, because we cannot withhold a medication considered clinically effective from research patients who are in acute distress or at risk of hurting themselves or others [50••]. Using the

study, antipsychotic (instead of a different antipsychotic) as the as-needed medication in the active arm as well as the placebo arm can help simplify this aspect of the research. Defining the study populations narrowly in terms of pathologies and severity, setting guidelines on which tools to use to screen and monitor for delirium, and setting robust statistical methods as a standard can help generate sound and homogenous research. Furthermore, broadening the research to the clinically pertinent aspects of delirium we discussed earlier can help better understand the possible utility of antipsychotics in delirium. Several important questions pertaining to the pharmacological prevention and management of delirium need to be answered to inform us clinically [8••].

A clinical guidance that is far removed from real-life clinical practices is likely to be ignored by clinicians. Even though we did not specifically explore clinician-related factors that may be contributing to gaps between knowledge and practice, we have anecdotally observed a tremendous need to improve the knowledge base and clinical practices pertaining to the use of antipsychotics in delirium. In some scenarios, antipsychotics may be over-utilized at the expense of non-pharmacological interventions, they may get over-used in dosage and duration, the possible beneficial effect of relatively well-studied antipsychotics may get generalized to antipsychotics that have not been well-studied, and their effectiveness and side effects may be difficult to monitor in view of the fluctuations in the patient's clinical status. These are important clinical aspects to research to bridge the gap between knowledge and clinical practices.

Our review should be read keeping in mind its limitations. We only focused on randomized studies. We mentioned two major studies that used historical control groups [36, 37] and several recent meta-analyses [10, 12, 13, 39, 40] but might have missed other studies. We did not elaborate on the strengths and weaknesses of individual studies because that was beyond the scope of this paper. We do selectively and conservatively recommend use of antipsychotics in delirium. This approach could have biased us to interpret research data to support our clinical point of view. Lastly, our review pertains to adults with delirium. Literature pertaining to the use of antipsychotics in children and adolescents with delirium is quite limited [51] and cannot be integrated with the literature from the adult population.

Conclusion

Current literature is too limited to reliably support or reject the use of antipsychotics in delirium. Until methodologically sound research pertinent to specific patient populations and clinical scenarios accumulates, we should use both the research literature and clinical expertise to formulate the best practice guidelines. Professional associations representing clinicians who provide care to patients with delirium can work together to provide clinical guidance that balances the limited research literature with clinical expertise. These associations can also provide guidance on the methodology of future research on prevention and treatment of delirium to help generate homogenous research that is suitable for meta-analyses and can be translated into clinical practice more consistently.

Compliance with ethical standards

Conflict of interest
The authors declare that they have no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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